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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/723,250 | 11/26/2003 | Thomas M. DiMauro | 3518.1024-000 | 6059 |

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| EXAMINER | |
|---|---|
| MAEWALL, SNIGDHA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/723,250 | DIMAURO ET AL. | |
| | Examiner | Art Unit | |
| | Snigdha Maewall | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05/27/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,7-10,21-25,27-30,60,70 and 89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-10,21-25,27-30,60,70 and 89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/27/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Receipt of Applicants' amendments /remarks, IDS and amended claims filed on 05/27/08 is acknowledged.

Claims 6, 26 and 57-58 have been canceled.

New claims 90-91 have been added in this application.

Claims 90 has been withdrawn from consideration since sustained release delivery device was drawn to non elected group (Applicant had elected only group 1 to be prosecuted as per response to restriction election dated 03/23/07).

Claim 91 has been withdrawn from consideration since applicant has constructively elected estrogen as highly specific cytokine antagonist that inhibits TNF-alfa.

Accordingly, claims **1-5, 7-10, 21-25, 27-30, 60, 70 and 89** are being examined on the merits herein.

### *Claim Rejections - 35 USC § 112*

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating an uncoupled resorbing bone or osteoporosis comprising administration of highly specific

cytokine antagonist that inhibits TNF-α such as estrogen , does not reasonably provide enablement for all other high specificity cytokine antagonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: l) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount &direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 73 l, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Independent claims 1, 21, 70 and 89 recite a method for treating an uncoupled resorbing bone or osteoporosis comprising administration of highly specific cytokine antagonist that inhibits TNF-α. The claim is very broad in scope and as recited reads on several cytokine antagonists, rather than just for estrogen for which the specification is enabled.

The nature of the invention is drawn to a method for treating uncoupled resorbing bone or osteoporosis comprising administration of highly specific cytokine antagonist that inhibits TNF-α .

Applicant's claims are drawn to incredibly broad super-genera of antagonists. Prior art teaches antagonists in the form of polypeptides (i.e. soluble receptors to the cytokine ligands), small molecule inhibitors (i.e. thalidomide, which is well known in the

art to inhibit TNF-alfa [see for example, Banerjee US PreGrant Publication 2004/0126372 A l, published 1 July 2004, benefit to 19 June 2002, paragraph 0383]. Each of these separate groups of cytokine antagonists are, in and of themselves, separate and distinct generas that each contains numerous species, directed to distinct structural and functionally independent cytokines and/or their receptors.

The level of skill of those in the art is extremely high due to the multifactorial parameters necessary to determine which cytokines are involved in which disease processes. As such, the breadth of the claims is excessive in light of the disclosure and what is known in the art. It would require undue experimentation by the skilled artisan to determine to which of the known cytokines antagonist which inhibits TNF-alfa to treat osteoporosis.

There is one working example of the claimed method. However, the example is disclosed as being "a non-limiting prophetic example" describing the administration of estrogen. Although working examples are not required, they are helpful in determining the predictability of a claimed method. In the instant case, the one working example provides a teaching of how to administer one species of high specificity cytokine antagonist such as estrogen.

However, due to the large numbers of other high specificity cytokine antagonists, as discussed supra, undue experimentation would be required in order to use the invention within the full scope of the claims.

Due to the large quantity of experimentation necessary to identify a high specificity antagonist, the lack of direction/guidance presented in the specification regarding same, the complex nature of the functional mechanisms associated with the various genera of cytokine antagonists, the state of the prior art which recognizes the unpredictability of targeting different cytokines and whether inhibition of different cytokines would be effective in treating osteoporosis, and the breadth of the claims,
undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
Recitation of the term highly in claims 1, 21, 70 and 89 renders the claim indefinite. The term is relative term. Appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radomsky (US 5,942,499) in view of Cullis Hill (USP 6,593,310) and Boyle et al. (US 2003/0207827) and further in view of Trieu et al. (US 2002/0026244).

Radomsky teaches a bone growth-promoting composition comprising growth factors such as fibroblast growth factor and platelet-derived growth factor and their methods of use (column 1, lines 19, 35-36, and 61). The invention can be used in various sites of desired bone growth including vertebral compression fractures and in pathological bone defects associated with osteoporosis (column 2, lines 50 and 55-58). The invention describes an injectable mixture of growth factor for intraosseous, or within bone, administration (column 12, lines 5-12).

The reference does not teach administration of anti-resorptive agent (estrogen as claimed) or the combination of administration of both, an effective amount of bone forming agent and highly specific cytokine antagonist that inhibits TNF-alfa (estrogen as claimed). To that end Cullis et al. and Boyle et al .both teach administering estrogen and bone forming agent.

Cullis teaches a method of treating osteoporosis comprising administering to a mammal a compound such as pentason polysulfate (abstract).The reference teaches that estrogen is known to reduce fractures and is an example of an anti-resorptive agent. (See column 1, lines 59-60). The reference teaches that in the process of treating osteoporosis an effective amount of polysulfated polysaccharide for instance calcium pentosan polysulfate can be given and optionally with the compounds such as fosamax, estrogen, calcium supplements, calcitrol etc (see column 4,lines 40-50).

Boyle et al. teach methods to treat bone diseases such as osteoporosis comprising osteoprotegrin, which is a polypeptide that plays a role in promoting bone accumulation (page 1, paragraphs [0001] and [0006]). Boyle et al. further teach treatment of osteoporosis in postmenopausal women and a direct relationship between osteoporosis and incidence of hip and neck fractures (page 9, paragraph [0095]). Osteoprotegrin acts as a receptor of the TNF family and prevents receptor-ligand interaction (page 4, paragraph [0043]). Osteoprotegrin also blocks interleukin (IL)1-α and IL1-β produced hypercalcemia (page 40, paragraph [0344]). Boyle et al. also teaches that estrogen is a known anti-resorptive agent (page 41, paragraph [0355]).

Radomsky and Cullis and Boyle do not teach the administration of the formulation into the bones.

Trieu teaches methods of implanting nucleus pulposus implants (page 1, paragraph [0007]). The method involves removal of the natural nucleus pulposus of the intravertebral disc and implantation of the nucleus pulposus of the invention (page 10, paragraph [0109]). The nucleus pulposus implant of the invention may contain

pharmacological agents used to treat osteoporosis including a bone morphogenetic protein, growth factors such as fibroblast growth factor and platelet-derived growth factor, and steroids (page 9, paragraphs [0101] and [0104]). The device of Trieu is placed adjacent to unfractured bones (page 9, paragraphs [0104]). Since the nucleus pulposus implant of the invention may contain pharmacological agents used to treat osteoporosis including a bone morphogenetic protein (see page 9, paragraph [0101]), it would be obvious that the device can be used to treat fractured bones such as a hip bone. Thus Trieu teaches local administration in between bones.

It would have been obvious to the one of ordinary skilled in the art at the time the invention was made to incorporate highly specific cytokine antagonist such as estrogen as taught by Cullis and Boyle et al. to the teachings of Radomsky et al. since the reference teaches advantage of the same in treating osteoporosis. One skilled in the art would have been motivated to administer in to the bone the formulation comprising the bone forming agent and estrogen because Trieu et al. successfully teach local administration of drug in between bones in order to treat osteoporosis.

***Response to Arguments***

8. Applicant's arguments with respect to claims 1-5, 7-10, 21-25, 27-30, 60, 70 and 89 have been considered but are moot in view of the new ground(s) of rejection.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Snigdha Maewall whose telephone number is (571)-272-6197. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-0580. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Snigdha Maewall/
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/Gollamudi S Kishore, Ph.D/
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